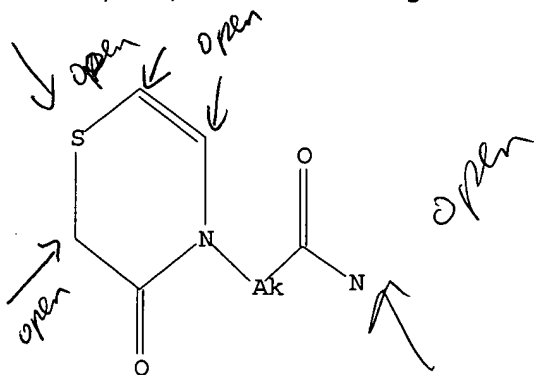


Broad search

Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 12:22:41 FILE 'REGISTRY'
SAMPLE SCREEN SEARCH COMPLETED - 2137 TO ITERATE

46.8% PROCESSED 1000 ITERATIONS 1 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
BATCH **COMPLETE**
PROJECTED ITERATIONS: 39968 TO 45512
PROJECTED ANSWERS: 1 TO 129

L2 1 SEA SSS SAM L1

=> s l1 sss full

FULL SEARCH INITIATED 12:22:48 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 44051 TO ITERATE

100.0% PROCESSED 44051 ITERATIONS 16 ANSWERS
SEARCH TIME: 00.00.01

L3 16 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	155.42	155.63

FILE 'CAPLUS' ENTERED AT 12:22:57 ON 14 DEC 2004
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FILE COVERS 1907 - 14 Dec 2004 VOL 141 ISS 25
FILE LAST UPDATED: 13 Dec 2004 (20041213/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> s l3

L4 2 L3

=> d ibib abs hitstr tot

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:

2001:78369 CAPLUS

DOCUMENT NUMBER:

134:131554

TITLE:

Preparation of novel thiazine or pyrazine derivatives as chymase inhibitors

INVENTOR(S):

Matsumoto, Junzo; Nishimura, Kazuo; Ban, Masakazu; Fujimura, Ken-ichi; Kobayashi, Naoyuki; Hori, Masanori; Honda, Takahiro

PATENT ASSIGNEE(S):

Santen Pharmaceutical Co., Ltd., Japan; Matsumoto, Eiko

SOURCE:

PCT Int. Appl., 278 pp.

DOCUMENT TYPE:

CODEN: PIXXD2

LANGUAGE:

Patent

FAMILY ACC. NUM. COUNT:

Japanese

PATENT INFORMATION:

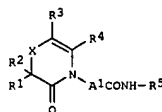
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WO 2001007419	A1	20010201	WO 2000-JP4964	20000726
W:	AZ, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RM:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2380218	AA	20010201	CA 2000-2380218	20000726
JP 2001097957	A2	20010410	JP 2000-224667	20000726
EP 1211249	A1	20020605	EP 2000-949890	20000726
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
US 6713472	B1	20040330	US 2002-31540	20020118
US 2004097496	A1	20040520	US 2003-713891	20031113
PRIORITY APPLN. INFO.:			JP 1999-210907	A 19990726
			WO 2000-JP4964	W 20000726
			US 2002-31540	A3 20020118

OTHER SOURCE(S):

MARPAT 134:131554

GI

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



AB Novel compds. having as the main skeleton 3-oxo-3,4-dihydro-2H-1,4-thiazine or 2-oxo-1,2,3,4-tetrahydropyrazine, which are represented by general formula (I); wherein X = S, R6-(A2)n-N; R1, R2 = H, lower alkyl, cycloalkyl, cycloalkyl, aryl; R3, R4 = H, lower alkyl, cycloalkyl, aryl, heteroaryl; R5 = H, lower alkyl, cycloalkyl, aryl, A3-R4-R7; wherein R6 = H, lower alkyl, cycloalkyl, HO, lower alkoxy, aryl, aryloxy, heteroaryl; R7 = H, lower alkyl, HO, lower alkoxy, aryl, aryloxy, NH2, lower alkylamino, arylamino, aromatic or nonarom. heterocyclyl; n = 0,1; A1 =

lower alkylene; A2 = CO, SO2; A3 = lower alkylene; A4 = CO, oxalyl; the above lower alkyl is optionally substituted by halo, HO, lower alkoxy, aryl, or aryloxy; the above lower alkoxy or lower alkylene is optionally substituted by aryl, are prepared these compds. are useful for the treatment of chymase-related diseases such as myocardial infarction, heart

failure, vascular restenosis after PTCA, hypertension, diabetes complications, allergies, and asthma. (3S)-3-[[[(3R)-4-benzoyl-3-isopropyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrazin-1-yl]methyl]carbonyl]amino]-2-oxo-4-phenylbutanoic acid iso-Pr ester which showed IC50 of 0.20 + 10-6 M against chymase.

IT 322396-01-OP 322396-02-1P 322396-03-2P

322396-04-3P 322396-05-4P 322396-07-6P

322396-08-7P 322396-09-7P 322396-01-8P

322396-92-9P 322396-93-OP 322396-94-1P

322396-95-2P 322396-96-3P

RL: BAC (Biological activity or effector, except adverse); BSU

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of novel thiazine or pyrazine derivs. as chymase

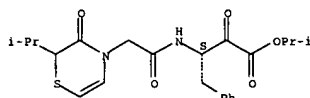
inhibitors for treatment of chymase-related diseases)

RN 322396-01-0 CAPLUS

CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

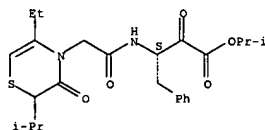
L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 322396-02-1 CAPLUS

CN Benzenebutanoic acid, β -[[[5-ethyl-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

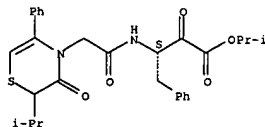
Absolute stereochemistry.



RN 322396-03-2 CAPLUS

CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-(1-methylethyl)-3-oxo-5-phenyl-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

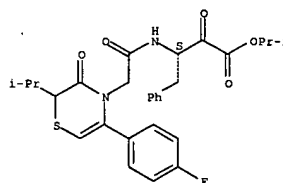


RN 322396-04-3 CAPLUS

CN Benzenebutanoic acid, β -[[[5-(4-fluorophenyl)-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

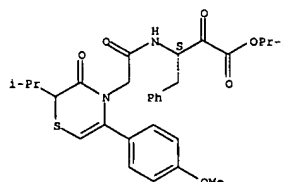
L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



RN 322396-05-4 CAPLUS

CN Benzenebutanoic acid, β -[[[2,3-dihydro-5-(4-methoxyphenyl)-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

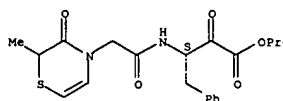
Absolute stereochemistry.



RN 322396-07-6 CAPLUS

CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-methyl-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

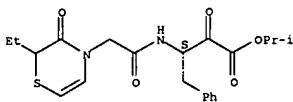
Absolute stereochemistry.



RN 322396-08-7 CAPLUS

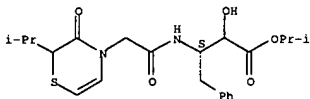
CN Benzenebutanoic acid, β -[[[2-ethyl-2,3-dihydro-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (BS)- (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
Absolute stereochemistry.



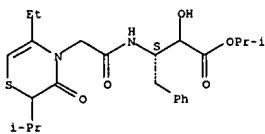
RN 322396-90-7 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 322396-91-8 CAPLUS
CN Benzenebutanoic acid, β -[[[5-ethyl-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



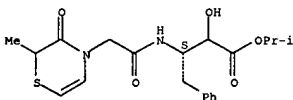
RN 322396-92-9 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-(1-methylethyl)-3-oxo-5-phenyl-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

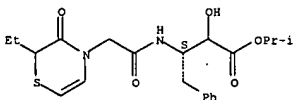
RN 322396-95-2 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-methyl-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



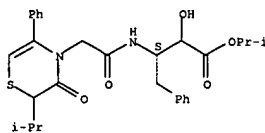
RN 322396-96-3 CAPLUS
CN Benzenebutanoic acid, β -[[[2-ethyl-2,3-dihydro-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



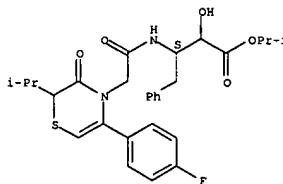
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



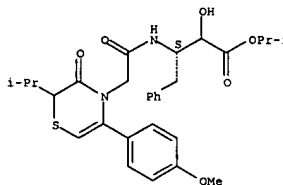
RN 322396-93-0 CAPLUS
CN Benzenebutanoic acid, β -[[[5-(4-fluorophenyl)-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 322396-94-1 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-5-(4-methoxyphenyl)-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



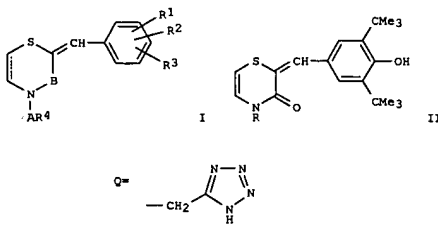
L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:954579 CAPLUS
DOCUMENT NUMBER: 123:340166
TITLE: Preparation of novel 2-benzylidenethiazine or 2-benzylidenethiomorpholine derivatives for treatment of cataracts
INVENTOR(S): Kawashima, Yoichi; Ota, Atsutoshi; Mibu, Hiroyuki
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 47 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 666261	A1	19950809	EP 1995-101413	19950202
EP 666261	B1	19970507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07258238	A2	19951009	JP 1995-8710	19950124
JP 2964382	B2	19991018		
US 5556841	A	19960917	US 1995-378502	19950126
CN 1112924	A	19951206	CN 1995-102904	19950129
NO 9500387	A	19950807	NO 1995-387	19950202
AT 152714	E	19970515	AT 1995-101413	19950202
CA 2141780	AA	19950805	CA 1995-2141780	19950203
FI 9500493	A	19950805	FI 1995-493	19950203
PRIORITY APPLN. INFO.:			JP 1994-12979	A 19940204

OTHER SOURCE(S): MARPAT 123:340166

GI



AB The title compound [I; R1 = (un)protected OH; R2 = lower alkyl; R3 = H, lower alkyl, (un)protected HO, lower alkoxy, and the said lower alkyl can be substituted by hydroxy, which can be protected by a hydroxy protective group, amino or lower alkylamino; R4 = CO2H which can be converted into

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 ester or amide, tetrazolyl, phosphono which can be converted into ester
 or

amide, sulfonyl which can be converted into ester or amide; A = alkylene;
 B = CO, CS or CH₂; the dotted line represents a single bond or double
 bond) are prepd. These compds. I have protein stabilizing effect and
 suppress lipid peroxide formation. Thus, lithiation of 1,4-thiazine with
 (Me₂CH)₂NLi in THF at -70° followed by addn. to
 3,5-di-tert-butyl-4-hydroxybenzaldehyde at -70°, mesylation with
 mesyl chloride in the presence of Et₃N in CH₂Cl₂ and elimination reaction
 gave 50% 2-benzylidene-1,4-thiazin-3-one deriv. (II; R = H). Alkylation
 of the latter compd. with bromoacetonitrile in the presence of NaH in THF
 gave II (R = CH₂CN) which underwent cycloaddn. reaction with NaN₃ in the
 presence of NH₄Cl in DMF at 110° to give II (R = Q) (III). III at
 10⁻⁴ M inhibited 99.5% the heat coagulation of bovine serum albumin in
 DMSO-0.2 M potassium phosphate buffer at 67° for 2 min. It in
 vitro suppressed 100% the lipid peroxide formation in microsomes of rat
 liver in the presence of Fe²⁺ and ascorbic acid in 0.04 M Tris buffer
 contg. 0.09 M KCl.

IT 170919-86-5P 170919-87-6P

RL: BAC (Biological activity or effector, except adverse); BSU

(Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);

BIOL (Biological study); PREP (Preparation); USES (Uses)

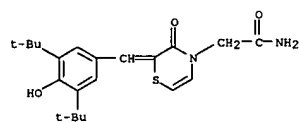
(preparation of benzylidenethiazine or -thiomorpholine derivs. as

protein

stabilizers and lipid peroxide formation inhibitors for treatment of
 cataracts)

RN 170919-86-5 CAPLUS

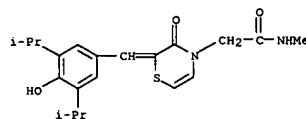
CN 4H-1,4-Thiazine-4-acetamide, 2-[[[3,5-bis(1,1-dimethylethyl)-4-
 hydroxyphenyl]methylene]-2,3-dihydro-3-oxo- (9CI) (CA INDEX NAME)

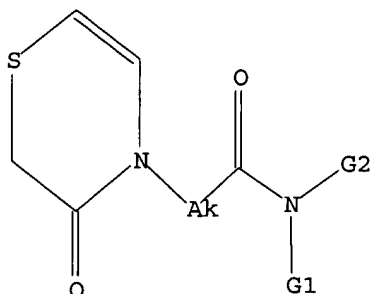


RN 170919-87-6 CAPLUS

CN 4H-1,4-Thiazine-4-acetamide, 2,3-dihydro-2-[[[4-hydroxy-3,5-bis(1-
 methylethyl)phenyl]methylene]-N-methyl-3-oxo- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)





G1 H, Me

G2 H, Ak, Cb, CH₂, CH

Structure attributes must be viewed using STN Express query preparation.

=> s l1

SAMPLE SEARCH INITIATED 08:21:04 FILE 'REGISTRY'

SAMPLE SCREEN SEARCH COMPLETED - 2137 TO ITERATE

46.8% PROCESSED 1000 ITERATIONS
 INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
 SEARCH TIME: 00.00.01

1 ANSWERS

FULL FILE PROJECTIONS: ONLINE **COMPLETE**
 BATCH **COMPLETE**

PROJECTED ITERATIONS: 39968 TO 45512
 PROJECTED ANSWERS: 1 TO 129

L2 1 SEA SSS SAM L1

=> s l1 sss full

FULL SEARCH INITIATED 08:21:10 FILE 'REGISTRY'

FULL SCREEN SEARCH COMPLETED - 44051 TO ITERATE

100.0% PROCESSED 44051 ITERATIONS
 SEARCH TIME: 00.00.01

16 ANSWERS

L3 16 SEA SSS FUL L1

=> file caplus

COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

155.42

155.63

FILE 'CAPLUS' ENTERED AT 08:21:17 ON 14 DEC 2004

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FILE COVERS 1907 - 14 Dec 2004 VOL 141 ISS 25
FILE LAST UPDATED: 13 Dec 2004 (20041213/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L4 2 L3

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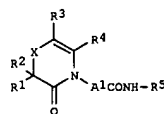
OWN
work

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
 ACCESSION NUMBER: 2001:78369 CAPLUS
 DOCUMENT NUMBER: 134:131554
 TITLE: Preparation of novel thiazine or pyrazine derivatives as chymase inhibitors
 INVENTOR(S): Matsumoto, Junzo; Nishimura, Kazuo; Ban, Masakazu; Fujimura, Ken-ichi; Kobayashi, Naoyuki; Hori, Masanori; Honda, Takahiro
 PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan; Matsumoto, Elko
 SOURCE: PCT Int. Appl., 278 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: Japanese
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001007419	A1	20010201	WO 2000-JP4964	20000726
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GN, GW, ML, MR, NE, SN, TD, TG			
CA 2380218	AA	20010201	CA 2000-2380218	20000726
JP 2001097957	A2	20010410	JP 2000-224667	20000726
EP 1211249	A1	20020605	EP 2000-949890	20000726
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL			
US 6713472	B1	20040330	US 2002-31540	20020118
US 2004097496	A1	20040520	US 2003-71389	20031113
PRIORITY APPLN. INFO.:			JP 1999-210907	A 19990726
			WO 2000-JP4964	W 20000726
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OTHER SOURCE(S): MARPAT 134:131554
 GI

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



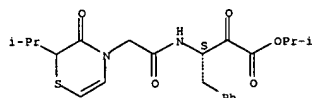
AB Novel compds. having as the main skeleton 3-oxo-3,4-dihydro-2H-1,4-thiazine or 2-oxo-1,2,3,4-tetrahydropyrazine, which are represented by general formula (I); wherein X = S, R6-(A2)n-N; R1, R2 = H, lower alkyl, cycloalkyl, cycloalkyl, aryl; R3, R4 = H, lower alkyl, cycloalkyl, aryl, heteroaryl; R5 = H, lower alkyl, cycloalkyl, aryl, A3-A4-R7; wherein R6 = H, lower alkyl, cycloalkyl, HO, lower alkoxy, aryl, aryloxy, heteroaryl; R7 = H, lower alkyl, HO, lower alkoxy, aryl, aryloxy, NH2, lower alkylamino, arylamino, aromatic or nonarom. heterocyclyl; n = 0,1; A1 = lower alkylene; A2 = CO, SO2; A3 = lower alkylene; A4 = CO, oxalyl; the above lower alkyl is optionally substituted by halo, HO, lower alkoxy, aryl, or aryloxy; the above lower alkoxy or lower alkylene is optionally substituted by aryl, are prepared. These compds. are useful for the treatment of chymase-related diseases such as myocardial infarction, heart failure, vascular restenosis after PTCA, hypertension, diabetes complications, allergies, and asthma. (3S)-3-([[(3R)-4-benzoyl-3-isopropyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrazin-1-yl]methyl]carbonyl]amino]-2-oxo-4-phenylbutanoic acid iso-Pr ester which showed IC50 of 0.20 + 10-6 M against chymase.

IT 322396-01-OP 322396-02-1P 322396-03-2P
 322396-04-3P 322396-05-4P 322396-07-6P
 322396-08-7P 322396-09-7P 322396-91-8P
 322396-92-8P 322396-93-OP 322396-94-1P
 322396-95-2P 322396-96-3P
 RL: BAC (Biological activity or effector, except adverse); BSU study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses) (preparation of novel thiazine or pyrazine derivs. as chymase inhibitors for treatment of chymase-related diseases)

RN 322396-01-0 CAPLUS
 CN Benzenebutanoic acid, β -[[(2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

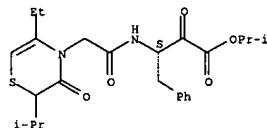
Absolute stereochemistry.

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



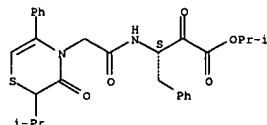
RN 322396-02-1 CAPLUS
 CN Benzenebutanoic acid, β -[[(5-ethyl-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 322396-03-2 CAPLUS
 CN Benzenebutanoic acid, β -[[(2,3-dihydro-2-(1-methylethyl)-3-oxo-5-phenyl-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

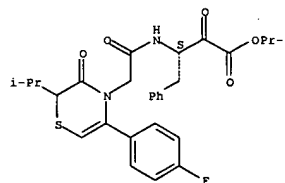
Absolute stereochemistry.



RN 322396-04-3 CAPLUS
 CN Benzenebutanoic acid, β -[[(5-(4-fluorophenyl)-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

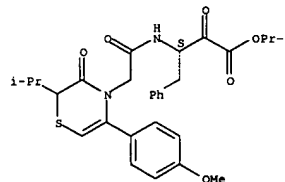
Absolute stereochemistry.

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



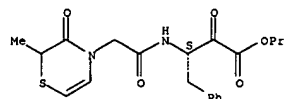
RN 322396-05-4 CAPLUS
 CN Benzenebutanoic acid, β -[[(2,3-dihydro-5-(4-methoxyphenyl)-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



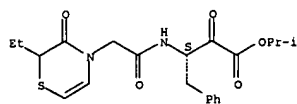
RN 322396-07-6 CAPLUS
 CN Benzenebutanoic acid, β -[[(2,3-dihydro-2-methyl-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



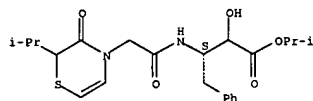
RN 322396-08-7 CAPLUS
 CN Benzenebutanoic acid, β -[[(2-ethyl-2,3-dihydro-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -oxo-, 1-methylethyl ester, (RS)- (9CI) (CA INDEX NAME)

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
Absolute stereochemistry.



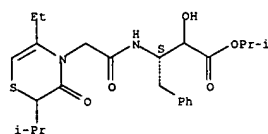
RN 322396-90-7 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 322396-91-8 CAPLUS
CN Benzenebutanoic acid, β -[[[5-ethyl-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



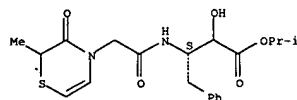
RN 322396-92-9 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-(1-methylethyl)-3-oxo-5-phenyl-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)

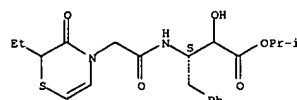
RN 322396-95-2 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-2-methyl-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 322396-96-3 CAPLUS
CN Benzenebutanoic acid, β -[[[2-ethyl-2,3-dihydro-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

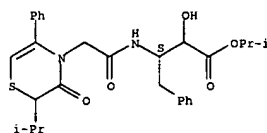
Absolute stereochemistry.



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

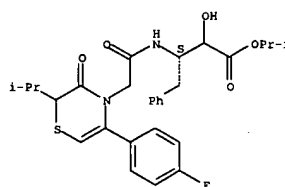
FORMAT

L4 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



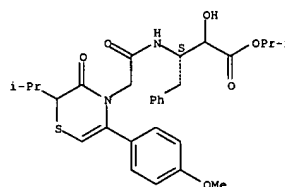
RN 322396-93-0 CAPLUS
CN Benzenebutanoic acid, β -[[[5-(4-fluorophenyl)-2,3-dihydro-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 322396-94-1 CAPLUS
CN Benzenebutanoic acid, β -[[[2,3-dihydro-5-(4-methoxyphenyl)-2-(1-methylethyl)-3-oxo-4H-1,4-thiazin-4-yl]acetyl]amino]- α -hydroxy-, 1-methylethyl ester, (9S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



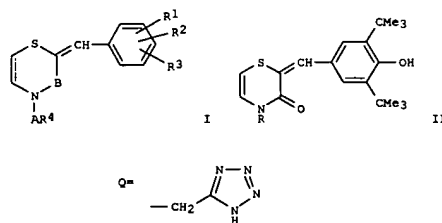
L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1995:954579 CAPLUS
DOCUMENT NUMBER: 123:340166
TITLE: Preparation of novel 2-benzylidenethiazine or 2-benzylidenethiomorpholine derivatives for treatment of cataracts
INVENTOR(S): Kawashima, Yoichi; Ota, Atsutoshi; Mibu, Hiroyuki
PATENT ASSIGNEE(S): Santen Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 47 pp.
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 666261	A1	19950809	EP 1995-101413	19950202
EP 666261	B1	19970507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07258238	A2	19951009	JP 1995-8710	19950124
JP 2964382	B2	19991018		
US 5556841	A	19960917	US 1995-378502	19950126
CN 1112924	A	19951206	CN 1995-102904	19950129
NO 9500387	A	19950807	NO 1995-367	19950202
AT 152714	E	19970515	AT 1995-101413	19950202
CA 2141780	AA	19950805	CA 1995-2141780	19950203
FI 9500493	A	19950805	FI 1995-493	19950203
PRIORITY APPLN. INFO.:				JP 1994-12979 A 19940204

OTHER SOURCE(S): MARPAT 123:340166

GI

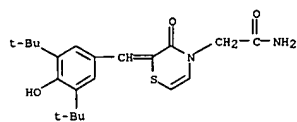


AB The title compound [I: R1 = (un)protected OH; R2 = lower alkyl; R3 = H, lower alkyl, (un)protected HO, lower alkoxy, and the said lower alkyl can be substituted by hydroxy, which can be protected by a hydroxy protective group, amino or lower alkylamino; R4 = CO2H which can be converted into

12/14/2004

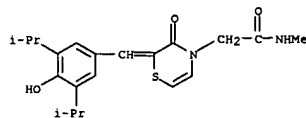
Habte

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)
 ester or amide, tetrazolyl, phosphono which can be converted into ester
 or
 amide, sulfonyl which can be converted into ester or amide; A = alkylene;
 B = CO, CS or CH₂; the dotted line represents a single bond or double
 bond] are prepd. These compds. I have protein stabilizing effect and
 suppress lipid peroxide formation. Thus, lithiation of 1,4-thiazine with
 (Me₂CH)₂NLi in THF at -70° followed by addn. to
 3,5-di-tert-butyl-4-hydroxybenzaldehyde at -70°, mesylation with
 mesyl chloride in the presence of Et₃N in CH₂Cl₂ and elimination reaction
 gave 50% 2-benzylidene-1,4-thiazin-3-one deriv. (II; R = H). Alkylation
 of the latter compd. with bromoacetonitrile in the presence of NaH in THF
 gave II (R = CH₂CN) which underwent cycloaddn. reaction with NaN₃ in the
 presence of NH₄Cl in DMF at 110° to give II (R = Q) (III). III at
 10-4 M inhibited 99.5% the heat coagulation of bovine serum albumin in
 DMSO-0.2 M potassium phosphate buffer at 67° for 2 min. It in
 vitro suppressed 100% the lipid peroxide formation in microsomes of rat
 liver in the presence of Fe²⁺ and ascorbic acid in 0.04 M Tris buffer
 contg. 0.09 M KCl.
 IT 170919-86-5P 170919-87-6P
 RL: BAC (Biological activity or effector, except adverse); BSU
 (Biological
 study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
 BIOL (Biological study); PREP (Preparation); USES (Uses)
 (preparation of benzylidenethiazine or -thiomorpholine derivs. as
 protein
 stabilizers and lipid peroxide formation inhibitors for treatment of
 cataracts)
 RN 170919-86-5 CAPLUS
 CN 4H-1,4-Thiazine-4-acetamide, 2-[[3,5-bis(1,1-dimethylethyl)-4-
 hydroxyphenyl]methylene]-2,3-dihydro-3-oxo- (9CI) (CA INDEX NAME)



RN 170919-87-6 CAPLUS
 CN 4H-1,4-Thiazine-4-acetamide, 2,3-dihydro-2-[[4-hydroxy-3,5-bis(1-
 methylethyl)phenyl]methylene]-N-methyl-3-oxo- (9CI) (CA INDEX NAME)

L4 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN (Continued)



Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L4	2688	544/58.2, 514/227.5, 514/227.8, 540/544, 540/575, 540/598	USPAT	OR	OFF	2004/12/14 12:17
L5	346	chymase\$	USPAT	OR	OFF	2004/12/14 12:17
L6	6	I4 and I5	USPAT	OR	OFF	2004/12/14 12:17

 **PALM INTRANET**KH
Day : Tuesday
Date: 12/14/2004

Time: 12:19:35

Inventor Information for 10/713891

Inventor Name	City	State/Country
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<u>BAN, MASAKAZU</u>	OSAKA-SHI	JAPAN
<u>FUJIMURA, KEN-ICHI</u>	OSAKA-SHI	JAPAN
<u>KOBAYASHI, NAOYUKI</u>	OSAKA-SHI	JAPAN
<u>HORI, MASANORI</u>	OSAKA-SHI	JAPAN
<u>HONDA, TAKAHIRO</u>	OSAKA-SHI	JAPAN
<u>MATSUMOTO, JUNZO</u>	ASHIYA-SHI	JAPAN
<u>MATSUMOTO, EIKO</u>	ASHIYA-SHI	JAPAN

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PubMed Central☐ 1: Nippon Yakurigaku Zasshi. 1999 Oct;114 Suppl 1:41P-47P. Related Articles, Li**[Pathophysiological roles of chymase and effects of chymase inhibitor]**

[Article in Japanese]

Takai S, Jin D, Miyazaki M.

Department of Pharmacology, Osaka Medical College, Japan.

Human chymase forms angiotenin (ANG) I to ANG II, whereas the roles of ANG II generated by chymase and the effects of chymase inhibitors have been unclear. On the other hand, rat chymase could not convert ANG I to ANG II. In isolated rat arteries, the ANG I-induced vascular contraction was completely suppressed by angiotensin-converting enzyme (ACE) inhibitor only. However, 30% of ANG I-induced vascular contraction in isolated human arteries was suppressed by an ACE inhibitor, but the remainder was blocked by chymostatin. In hamster hypertensive models, ANG II formation by ACE, but not by chymase, in vascular tissues plays an important role in maintaining hypertension. ANG II formation also induces vascular remodeling such as neointima formation. After balloon injury of vessels in dog, chymase and ACE activities were significantly increased in the injured vessels. In this model, an ANG II receptor antagonist was effective in preventing neointimal formation after balloon injury of vessels in dog, but an ACE inhibitor was ineffective. In dog grafted veins, the activities of chymase and ACE in the grafted vein were significantly increased 15- and 2-fold, respectively, compared with those in the symmetrical veins. The intimal area of the grafted vein was reduced by a chymase inhibitor. Therefore, chymase-dependent ANG II formation plays an important role in the proliferative response, and chymase inhibitors may appear useful for preventing vascular proliferation.

Publication Types:

- Review

PMID: 10629853 [PubMed - indexed for MEDLINE]

 Abstract Text